REMARKS

Claims 1-33 and 47-48 are pending in the application. Claims 34-46 have been cancelled, without prejudice. Claims 2, 3, 9, 12, and 22 have been amended. Claims 1, 33, 47, and 48 are the only independent claims.

The specification has been amended to correct a typographical error and to delete a hyperlink. The typographical error relates to substituting "$F(ab')_2$" (the name of a well known type of antibody fragment) in place of "$F(abN)_2$" (a term with no known meaning). A skilled artisan would recognize "$F(abN)_2$" as a misspelling of "$F(ab')_2$", both in the context of antibody fragments and in light of use of the correct term in the specification, for example, at page 13, line 13.

Claims 2, 3, 9, 12, and 22 have been amended. No new matter is added by the amendments. Support for the amendments is found at least in the specification at page 10, lines 18-20 (amendment to claim 22); page 31, lines 5-7 (amendment to claim 2); page 10, lines 11-16 (amendment to claim 3); and page 16, lines 17-21 (amendment to claims 9 and 12). None of these amendments limits the scope of the claims, each amended claim merely reciting in an alternative form the subject matter that was previously recited in the originally-filed claims.

Pursuant to 37 C.F.R. § 1.121, a marked up version of the amended portions of the specification, showing the changes made, is enclosed herewith on a separate paper.

No new matter is added by the amendments made herein to the claims and the specification.

Each of the Examiner's objections or rejections is addressed below in the order they were presented in Paper No. 9.

I. Filing Date.

The Applicant notes that a Request for Reconsideration of Petition Pursuant to 37 C.F.R. § 1.110(d), requesting reconsideration of the Petition was filed April 8, 2002.

II. Formal Drawings.

At page 2 of Paper No. 9, the Examiner indicates that the draftsperson requires submission of corrected drawings. Corrected drawings are enclosed herewith, accompanied by a separate transmittal letter addressed to the Official Draftsperson. The corrected drawings are fully compliant with 37 C.F.R. § 1.84, and the only changes to the drawings relate to corrections of informalities. No substantive changes to the drawings were made. Accordingly, the Applicant respectfully requests that the Examiner and Draftsperson reconsider and withdraw the objection to the drawings.

III. Information Disclosure Statement.

At page 3 of Paper No. 9, the Examiner has acknowledged the Applicant's Information Disclosure Statements (IDSs) filed January 19, 2001, and June 29, 2001. With Paper No. 9, the Examiner has enclosed copies of the Forms 1449 enclosed with those IDSs, having initialed only those references which the Examiner was able to supply.

Enclosed with this response, the Applicant has provided copies of those references cited on the returned Forms 1449 which have not yet been made of record (initialed) by the Examiner. A list of all such references is attached hereto as Appendix A, along with a copy of the IDSs and Forms 1449, as filed.

It is respectfully requested that the Examiner consider each of these references, make them of record in the application, and return a fully initialed copy of each Form 1449 to the Applicant with the next Office Action.

IV. Objections to the Specification.

At page 3 of Paper No. 9, the Examiner has objected to the specification and claim 22 because of a typographical error wherein "$F(abN)_2$" has been used in place of "$F(ab')_2$". The specification and claim 22 have been corrected accordingly.

At item 7, the Examiner has objected to the specification because it contains a hyperlink. The Applicant has deleted the hyperlink for the NCBI web page, previously found at page 18, line 24.

In view of the foregoing, it is respectfully requested that the Examiner reconsider and withdraw the objections to the specification.

V. Rejections Pursuant to 35 U.S.C. § 112, Second Paragraph.

At pages 3-4 of Paper No. 9, the Examiner has rejected claims 2-4 pursuant to 35 U.S.C. § 112, second paragraph, asserting that such claims are indefinite.

In claim 2, the Examiner asserts that "substantially only," renders the claim indefinite. Claim 2 has been amended by deleting "substantially only," and specifying that the anti-CD18 antibody binds specifically with the CD18 portion of the protein, but does not bind specifically with the non-CD18 portion of the protein. This amendment does not narrow the scope of the original claim. The Applicant contends that they do not need to provide a testable basis for identifying an antibody that binds specifically with "substantially only" the CD18 portion, because this phrase has been deleted from the claim. Methods of assessing whether an antibody binds specifically with a portion of an antigen are well known, and are disclosed in the specification, for example at page 11, line 10, through page 12, line 8.

The Examiner asserts that "similar to" in claim 3 is ambiguous. Claim 3 has been amended by deleting "similar to." Instead, claim 3 now recites that the anti-CD18 antibody is a competitive inhibitor of the binding of monoclonal antibody 1B4 to human CD18. Because antibodies having similar or identical binding specificities are competitive inhibitors of one another's binding to their common epitope, this amendment does not narrow the scope of the original claim. The Applicant contends that they do not need to provide a testable basis for identifying an antibody that "has an epitopic specificity which is the same as or similar to" that of antibody 1B4, because this phrase has been deleted from the claim. Methods of assessing whether one antibody is a

competitive inhibitor of another are well known in the art and disclosed in the specification, for example at page 10, lines 11-16.

The Examiner also asserts that claims 3 and 4 are indefinite because they recite a monoclonal antibody designated "1B4." The Examiner contends that "1B4" is an imprecise means of identifying the claimed antibody. The Applicant respectfully traverses this rejection. Recitation of monoclonal antibody 1B4 does not render the claim imprecise or indefinite. Antibody 1B4 was deposited by others with the ATCC, as an antibody obtainable from a specific cell line, which is identified by ATCC Accession No. HB-10164 as indicated in Table C on page 49 of the specification and in U.S. Patent 5,147,637 (Wright, of record, column 2, lines 60-64). Antibody 1B4 is therefore available to the public.

For the foregoing reasons, the Applicant contends that the Examiner's rejections pursuant to 35 U.S.C. § 112, first paragraph, have been overcome. Accordingly, it is requested that the Examiner reconsider and withdraw each rejection.

VI. Rejection Pursuant to 35 U.S.C. § 112, First Paragraph, Enablement - 1B4 Antibody.

At pages 4-5, the Examiner has rejected claims 3 and 4 pursuant to 35 U.S.C. § 112, first paragraph, asserting that such claims contain subject matter which is not enabled by the specification. Specifically, the Examiner believes that monoclonal antibody 1B4 is not known and readily available to the public as required by § 112. The Applicant respectfully traverses this rejection.

First, as discussed above, antibody "1B4" can be obtained from a specific cell line, which is identified by ATCC Accession No. HB-10164, as set forth in Table C, on page 49 of the specification. The Examiner highlights that a mistaken reference to cell line "TIB-10164" appears in the specification at page 45, lines 21-23. The Applicant includes herewith a copy of an ATCC database search performed using accession number TIB-10164. The search reveals that no such deposit exists. The Applicant respectfully contends that, faced with the correct accession number (in Table C on page 49) and an

inoperative accession number (at page 45, lines 21-23), the skilled artisan would select the correct accession number and recognize the other as a typographical error. The Applicant believes that no formal declaration of these facts is necessary. Accordingly, the Applicant asserts that claims reciting monoclonal antibody 1B4 are fully enabled by the specification.

Accordingly, for the reasons above, it is respectfully requested that the Examiner reconsider and withdraw the rejection for lack of enablement.

VII. Rejection Pursuant to 35 U.S.C. § 112, First Paragraph, Enablement - "Similar to."

At page 5, item 13, the Examiner has rejected claim 3 pursuant to 35 U.S.C. § 112, first paragraph, asserting that the specification does not enable methods employing an antibody having an epitopic specificity that is "similar to" that of monoclonal antibody 1B4.

Claim 3 has been amended to delete those portions of the claim which refer to antibodies that have specificity that is "similar to" that of 1B4; therefore the Examiner's rejection is no longer applicable. However, the Applicant traverses this rejection should the Examiner chose to apply it to amended claim 3.

Claim 3, as amended, is fully supported by the specification. Methods for determining whether an antibody is a competitive inhibitor of binding between the 1B4 monoclonal antibody and a portion of the CD18 protein are described in the specification, for example, at page 10, lines 6-23, and further are well-known in the art. *See, for example*, Rucker *et al.*, 1996, Cell 87:437-446.

Therefore, for at least the reason given above, it is respectfully requested that the Examiner withdraw the rejection for lack of enablement of claim 3 and not apply it to the newly amended claim 3.

VIII. Rejection Pursuant to 35 U.S.C. § 112, First Paragraph, Proteins and Ligands.

In item 14, on page 6 of the Office Action, the Examiner rejects claims 1-33, 47, and 48 pursuant to 35 U.S.C. § 112, first paragraph. The Examiner objects that the specification does not sufficiently identify all mammalian proteins that comprise CD18 or the ligands of such proteins, and that the rejected claims are not enabled for that reason. The Applicant believes that the Examiner's rejection is inapplicable to the claims, as amended. In the ensuing paragraphs, the Applicant separately addresses the Examiner's rejection as it relates to proteins and their ligands.

With regard to mammalian proteins, the Examiner recognizes that several CD18-containing proteins were known in the art, but objects that the specification does not indicate whether the known proteins represent all of the CD18-containing surface proteins for any mammalian species. The Examiner also indicates that she believes that undue experimentation would be necessary to identify a "representative number" of CD18-containing proteins.

The Examiner does not appear to question that the specification teaches a skilled artisan how to use a CD18-containing protein once it is identified, and the Applicant assumes that the Examiner's rejection is not based on a contention that the Applicant has failed to meet the how-to-use requirements of enablement. The Applicant also contends that the specification adequately teaches how to use antibodies that bind specifically with CD18 to at least inhibit stenosis, as disclosed in the specification at page 7, line 12, through page 8, line 3. Instead, the Examiner's comments suggest that the Examiner believes that the Applicant has not adequately taught one how to make a set of CD18-containing proteins, ligands of CD18-containing proteins, or both, beyond the examples given, commensurate with the scope of the rejected claims. The Examiner's concern appears misplaced for the following reasons.

The Applicant is not claiming CD18-containing proteins or their ligands. Instead, the Applicant claims methods of using an antibody that has the property that it binds with the CD18 portion of a CD18-containing protein (see claim 1). Thus, the Applicant's specification need only teach how to make CD18-binding antibodies to the

extent that the antibodies are employed in the claimed methods. A skilled artisan would recognize that one could generate antibodies that bind with the CD18 portion of a CD18-containing mammalian protein by immunizing a vertebrate with the protein (i.e., one needs to have the protein to do this). However, that is only one way the antibodies recited in the claim can be made. As described in the specification, for example at page 11, line 10, through page 12, line 8, numerous methods can be used to generate antibodies which bind with the CD18 portion of a protein. These methods include, for example, screening of libraries of recombinant antibodies (as described in the specification at page 12, lines 26-28) and immunization with CD18 of transgenic animals that express human antibodies (e.g., the Abgenix, Inc. XENOMOUSE™, as described in the specification at page 12, lines 3-8). The Applicant respectfully contends that the specification discloses, and the skilled artisan recognizes, many ways of making the set of antibodies recited as being used in the rejected method claims.

With regard to ligands of mammalian CD18-containing proteins, claim 9 has been amended to clarify that the antibody recited in the claims inhibits binding of the ligand with the CD18 portion of the CD18-containing protein. Numerous ligands of CD18 are known, and the specification discloses methods of assessing whether an antibody inhibits CD18-ligand binding (e.g., at page 16, line 23, through page 23, line 15) and methods of identifying additional CD18 ligands (e.g., at page 23, line 17, through page 28, line 13). The Applicant respectfully contends that these portions of the specification adequately teach the skilled artisan how to make the antibodies recited in the claims. Because the Applicant is not claiming the ligands themselves, the Applicant is not required, as the Examiner suggests, to describe a "representative number" of such ligands in order to enable use of the antibodies that are recited in the claims. The specification enables one to make antibodies that inhibit binding between CD18 and any known ligand thereof in accordance with the claimed methods.

For the foregoing reasons, reconsideration and withdrawal of the Examiner's rejection of claims 1-33, 47, and 48 pursuant to 35 U.S.C. § 112, first paragraph (based on purported lack of enablement) are respectfully requested.

IX. Rejection Pursuant to 35 U.S.C. § 112, First Paragraph - Written Description.

In item 15, on pages 6 and 7 of the Office Action, the Examiner rejects claims 1-33, 47, and 48 pursuant to 35 U.S.C. § 112, first paragraph. In the Examiner's view, the specification does not demonstrate that the Applicant was in possession of a representative number of mammalian CD18-containing proteins or in possession of a representative number of ligands of such proteins. The Examiner suggests that the Written Description Guidelines indicate that the Applicant must demonstrate possession of these genera in order to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. The Applicant believes that the Examiner mis-applies the Written Description Guidelines.

What is required by the written description requirement of 35 U.S.C. § 112 is a written description of the invention (M.P.E.P. § 2161, second paragraph). The invention is, of course, defined by the claims (M.P.E.P. § 2163.02, first paragraph).

The Applicant is not claiming mammalian CD18-containing proteins or ligands of these proteins. Thus, the Applicant is not required to demonstrate possession of every species, or even a representative number of species, of these two genera of compounds. The claims recite methods of using CD18-binding antibodies. Thus, the Applicant's disclosure need only describe the genus of CD18-binding antibodies (and how they are to be used).

Several CD18-binding antibodies were known as of the time the application was filed (e.g., antibodies designated 1B4, R15.7, and 60.3, as described in the specification at page 9, lines 8-15). The specification also teaches how to make other CD18-binding antibodies (e.g., at page 11, line 10, through page 12, line 8). Furthermore, methods of making antibodies against a defined target (e.g., CD18 or epitopes thereof) were well known in the art when the application was filed. Thus, the skilled artisan would recognize that the methods disclosed in the specification can be used equally with presently known CD18-containing proteins and any CD18-containing protein that is discovered in the future. The skilled artisan would recognize from the

specification's description of several examples of CD18-binding antibodies and of the relevant structural characteristics (e.g., having one or more variable regions that binds with CD18) of other useful antibodies, that the Applicant was in possession of the entire genus that is recited in the claims - namely CD18-binding antibodies.

The Applicant believes that the Examiner has mis-applied the written description requirement of 35 U.S.C. § 112, first paragraph, by requiring a written description of genera of compounds (i.e., CD18-containing proteins and their ligands) that are not claimed. The specification adequately describes the anti-CD18 antibodies that are recited in the claims, which is what the written description requirement mandates. For these reasons, the Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 1-33, 47, and 48 for alleged failure to comply with the written description requirement.

X. Rejection Pursuant to 35 U.S.C. § 102(b).

At page 8, item 17 of Paper No. 9, the Examiner has rejected claims 1-3, 5-20, 24, 26-33, 47, and 48 pursuant to 35 U.S.C. § 102(b) over U.S. Patent No. 5,997,867 ("Waldmann"), as evidenced by Rogers et al. In the Examiner's view, Waldmann teaches administering a humanized anti-CD18 antibody to a human in order to treat a patient afflicted with various leukocyte-mediated disorders. The reason that the Examiner believes that Waldmann is relevant to the pending claims is that Waldmann discloses using anti-CD18 antibodies in the context of treating reperfusion damage following thrombolytic therapy. The Applicant believes that the Examiner confuses reperfusion damage with the very different phenomena of stenosis and restenosis.

Reperfusion damage is a type of acute injury that occurs following resumption of oxygenated blood supply to a previously ischemic tissue. As indicated in the enclosed review by Verma et al., reperfusion injury is characterized by rapid (i.e., within a few minutes following reperfusion - see Verma p. 2333, right column, first two paragraphs) production of excessive quantities of reactive oxygen species, likely mediated by the presence of leukocytes in or on the reperfused tissue. Injury to

reperfused tissue occurs within minutes to hours following reperfusion, as indicated in the enclosed abstracts by Olivas et al. (which notes that most reperfusion injury occurred by 8 hours following reperfusion) and Horwitz et al. (which indicates that reperfusion injury occurs for the first 3 hours following reperfusion, but decreases thereafter).

Reperfusion injury has several characteristic manifestations, including i) necrosis of, ii) prolonged post-ischemic dysfunction of, and iii) microvascular dysfunction in the reperfused tissue (See Verma, page 2332). However, intimal thickening and hyperplasia (i.e., distinguishing characteristics of stenosis and restenosis) of the reperfused tissue or of blood vessels within the reperfused tissue is not a characteristic manifestation of reperfusion injury. Thus, a skilled artisan would not consider the disclosures in Waldmann relating to use of anti-CD18 antibodies to treat or prevent reperfusion injury to have any relevance to treatment or prevention of vascular stenosis/restenosis.

The Examiner asserts (Office Action, page 8, second paragraph of item 17) that reperfusion damage inherently occurs in angioplasty and stent placement. This is not accurate. As Verma indicates (see the paragraph bridging the columns on page 2332), cardiomyocytes (like other cells) are able to tolerate brief periods of ischemia, such as those associated with angioplasty, without exhibiting reperfusion damage. Stent placement is ordinarily not a cause of reperfusion, but instead is performed in order to maintain the patency of a blood vessel that supplies a non-ischemic tissue.

In contrast to reperfusion damage, stenosis and restenosis are conditions that develop over a relatively long period of time and are characterized by vascular intimal thickening and hyperplasia. Stenosis and restenosis are not manifested until months after the onset of stenosis- or restenosis-inducing conditions (e.g., not until months after arterial stent placement). Reperfusion damage occurs within seconds or minutes following resumption of blood supply to an ischemic tissue. There is no disclosure or suggestion in Waldmann that the effectiveness of anti-CD18 antibodies for treating or inhibiting short-term vascular reperfusion damage would lead a skilled artisan to believe that anti-CD18 antibodies exhibit any effectiveness for inhibiting or treating

long-term vascular stenosis or restenosis. Thus, Waldmann does not disclose or suggest that anti-CD18 antibodies can be used to inhibit stenosis or restenosis.

The Examiner's comments (e.g., in the final two paragraphs on page 8 of the Office Action) suggest that the Examiner believes that there is significant overlap between patients who sustain reperfusion damage and patients in whom stenosis or restenosis occurs, and that this assertion is supported by Rogers (WO 98/42360). These assertions are not accurate.

Reperfusion injury occurs rapidly following performance of a procedure that restores blood supply to a tissue (e.g., cardiovascular reperfusion injury occurs rapidly after clot dissolution in thrombolytic therapy). By contrast, there is substantially no manifestation of stenosis or restenosis in patients exposed to stenosis- or restenosis-inducing conditions until at least weeks or months after the onset of the conditions (e.g., restenosis can generally not be detected until weeks or months after vascular stent placement - see the enclosed abstracts by Koning et al. {peak restenosis occurred about 3 months following angioplasty} and Schwartz et al. {peak intimal smooth muscle cell proliferation occurred about 16 days following arterial injury}).

Contrary to the Examiner's assertion, Rogers does not disclose or suggest that reperfusion damage inherently occurs when vascular blood flow is increased. Instead, Rogers simply discloses that traumatic injury to vascular walls can lead, over an extended period of weeks or months, to intimal thickening that is characteristic of stenosis and restenosis. Furthermore, neither Rogers nor Waldmann discloses that treatment of reperfusion damage will have any inhibitory effect on stenosis or restenosis or vice versa.

A single patient may experience both reperfusion damage (within minutes) and restenosis (within weeks or months) following balloon angioplasty of an artery. The reperfusion damage occurs within hours, but restenosis cannot be detected for weeks or months (see the Koning et al. and Schwartz et al. abstracts). Waldmann discloses that reperfusion damage can be prevented by prophylactic administration of anti-CD18 antibody, and that the antibody can be administered to a patient "already suffering from"

a disease such as reperfusion injury in order to "cure or at least partially arrest or alleviate the disease" (column 9, line 41-47). Because the symptoms and consequences of reperfusion injury are manifested just minutes or hours after the injury is sustained, a skilled artisan would have no motivation to follow the disclosure of Waldmann in order to inhibit a condition (e.g., post-angioplasty restenosis) that does not develop until weeks or months after reperfusion injury is sustained.

For the foregoing reasons, the Applicant respectfully contends that a skilled artisan would not believe that Waldmann discloses or suggests administration of anti-CD18 antibody to a human in order to inhibit vascular stenosis or restenosis. The Examiner is requested to reconsider and withdraw the rejection of claims 1-3, 5-20, 24, 26-33, 47, and 48 pursuant to 35 U.S.C. § 102(b) in view of Waldmann.

XI. Rejections Pursuant to 35 U.S.C. § 103(a).

In items 18-20, the Examiner rejects claims 1-3, 5-33, 47, and 48 pursuant to 35 U.S.C. § 103(a) over Rogers in view of Waldmann, and claim 4 over Rogers in view of Waldmann and Wright. The Examiner recognizes that Rogers does not disclose use of an antibody that binds with the CD18 portion of a CD18-containing protein. The Examiner suggests that, at least in the absence of evidence to the contrary, it would have been obvious to use an anti-CD18 antibody (as described by Waldmann) in place of the antibodies disclosed in Rogers because Waldmann discloses that anti-CD18 antibodies can be used to treat certain leukocyte-mediated disorders such as reperfusion injury incurred following thrombolytic therapy. The Applicant respectfully suggests that the skilled artisan would not believe that the efficacy of anti-CD18 antibodies against reperfusion injury disclosed in Waldmann is predictive of any efficacy of the same antibodies against stenosis or restenosis. The Applicant addresses the two § 103(a) rejections separately in the following paragraphs.

In the rejection of claims 1-3, 5-33, 47, and 48, the Examiner recognizes that Rogers discloses that several leukocyte surface antigens comprise CD18 protein, and that stenosis/restenosis can be inhibited using antibodies that bind specifically with any of

those several surface antigens. However, contrary to the Examiner's assertion in the final paragraph on page 9 of the Office Action, Rogers does not disclose or suggest that an antibody that binds specifically with the CD18 portion of any of these cell surface antigens can be used to inhibit vascular stenosis/restenosis. In fact, at the time the present application was filed, the literature taught that an antibody that binds specifically with the CD18 portion of a leukocyte cell surface antigen DID NOT inhibit vascular restenosis following balloon angioplasty (Guzman et al., 1995, Coronary Artery Disease 6:693-701; cited on IDS and copy enclosed). Thus, the art available at the time the present application was filed indicated that the invention that is now claimed would not work.

The Examiner suggests that Waldmann, viewed in combination with Rogers overcomes the shortcomings of Rogers alone (at least for all pending claims other than claim 4). As discussed above in the section relating to the Examiner's rejection pursuant to 35 U.S.C. § 102(b), Waldmann teaches using an anti-CD18 antibody to treat various leukocyte-mediated disorders, including reperfusion injury that occurs following thrombolytic therapy. The Applicant points out that stenosis and restenosis are not reperfusion-type injuries, and that Waldmann does not disclose or suggest that anti-CD18 antibodies inhibit stenosis or restenosis. Waldmann contains no motivation that would cause the skilled artisan to even attempt to inhibit vascular stenosis or restenosis using an anti-CD18 antibody, and it contains no information that would cause a skilled artisan to believe that an anti-CD18 antibody could successfully inhibit vascular stenosis or restenosis even if administration of an anti-CD18 antibody were tried. Even if a skilled artisan were to combine Rogers and Waldmann, the skilled artisan would nonetheless conclude that anti-CD18 antibodies cannot be used to inhibit stenosis/restenosis in view of Guzman.

For the foregoing reasons, the Applicant respectfully contends i) that there is no motivation for the skilled artisan to combine Rogers and Waldmann; ii) that, even combined, Rogers and Waldmann do not teach that anti-CD18 antibodies can be used to inhibit vascular stenosis or restenosis; and iii) that, in view of what is disclosed in

Guzman, the skilled artisan would not make the intellectual leap that the Examiner suggests - that anti-CD18 antibodies disclosed by Waldmann would inhibit stenosis/restenosis in the manner of the antibodies disclosed by Rogers. The Examiner has therefore not set forth a prima facie case of obviousness. Reconsideration and withdrawal of the Examiner's rejection of claims 1-3, 5-33, 47, and 48 pursuant to 35 U.S.C. § 103(a) over Rogers in view of Waldmann are therefore respectfully requested.

The Examiner rejects claim 4 pursuant to 35 U.S.C. § 103(a) over Rogers in view of Waldmann and Wright. Wright discloses that antibody 1B4 is an anti-CD18 antibody. Claim 4 recites that the antibody used is 1B4. The Examiner's reasoning for rejecting claim 4 is the same as that stated above for the other claims rejected pursuant to 35 U.S.C. § 103(a), and the Applicant's counter-arguments are the same. Namely, i) no combination of the Rogers, Waldmann, and Wright references discloses that any anti-CD18 antibody (including 1B4) can be used to inhibit stenosis/restenosis; ii) there is no motivation to combine the references; and iii) the Guzman references teaches that even if one were to make the inferences suggested by the Examiner with regard to the cited references, anti-CD18 antibodies such as 1B4 would not inhibit stenosis/restenosis. Reconsideration and withdrawal of the § 103(a) rejection of claim 4 are also requested.

XII. Summary.

For the reasons set forth above, the Applicant respectfully contends that each of claims 1-33, 47, and 48 is in condition for allowance. Reconsideration and withdrawal of each of the Examiner's rejections are requested, and the Examiner is requested to issue a Notice of Allowance at the earliest possible time.

Respectfully submitted,

CHRISTOPHER J. HORVATH

22 July 2002
(Date)

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Enclosures:
Petition for Extension of Time
Marked-Up Copy of Replacement Specification Paragraphs
Clean Copy of Replacement Specification Paragraphs
Marked-Up Copy of Claims Amended
Clean Copy of Claims, as Amended
Corrected Formal Drawings (7 sheets) and Transmittal
Appendix A, listing references re-submitted herewith
Copy of ATCC® Database Search for TIB-10164
Verma et al., 2002, Circulation 105:2332-2336
Abstract of Olivas et al., 2001, Plast. Reconstr. Surg. 107(3):785-788
Abstract of Horwitz et al., 1999, J. Cardiovasc. Pharmacol., 33(1):19-29
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Abstract of Koning et al., 1989, Arch. Mal. Coeru. Vaiss. 82(2):177-184
Abstract of Schwartz et al., 1996, Int. J. Cardiol. 53(1):71-80
References listed in Appendix A

Appendix A

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Inoue et al., 1996, J. Amer. Coll. Cardiol. 28:1127-1133
Inoue et al., 1998, Thromb. Haemost. 79:54-58
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Mickelson, et al., 1999, J. Am. Coll. Cardiol. 33(1):97-106 (abstract only)
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Topol, et al., 1994, Lancet 343:881-886
Wautier, 1989, J. Mal. Vasc. 14 Suppl A 13-16

Marked-Up Copy of Replacement Specification Paragraphs Filed with the Amendment Responding to the Office Action Dated 20 February 2002

Please delete the paragraph at page 4, lines 6 to 8, and substitute in place thereof the paragraph amended to read as follows.

The anti-CD18 antibody used in this method can, for example, be a whole antibody, an antibody fragment (e.g. one of a Fv, Fab, Fab', or ~~F(abN)$_2$~~-F(ab')$_2$ fragment), a chimeric antibody, a humanized antibody, or a fully human antibody.

Please delete the paragraph at page 13, lines 9 to 17, and substitute in place thereof the paragraph amended to read as follows.

For example, anti-CD18 antibody fragments capable of binding to a mammalian CD18 or a portion thereof, including Fv, Fab, Fab' and ~~F(abN)$_2$~~-F(ab')$_2$ antibody fragments, are encompassed by the invention. Such fragments can be produced by enzymatic cleavage of whole anti-CD18 antibodies or by recombinant techniques, for example. For instance, papain or pepsin cleavage can generate Fab or F(ab')$_2$ fragments, respectively. Antibodies can also be produced in a variety of truncated forms using antibody genes in which one or more stop codons has been introduced upstream of the natural stop site. For example, a chimeric gene encoding a F(ab')$_2$ heavy chain portion can be designed to include DNA sequences encoding the CH_1 domain and hinge region of the heavy chain.

Please delete the paragraph at page 18, lines 14 to 28, and substitute in place thereof the paragraph amended to read as follows.

In one embodiment, a functional variant of mammalian CD18 shares at least about 85% sequence identity with the corresponding mammalian CD18 (e.g. human CD18, as described in GenBank accession number NM_000211, or another primate CD18), preferably at least about 90% sequence identity, and more preferably at least about 95% sequence identity with said mammalian CD18. In another embodiment, a functional fusion protein comprises a first moiety which shares at least about 85% sequence identity with the corresponding mammalian CD18, preferably at least about 90% sequence identity, and more preferably at least about 95% sequence identity with the mammalian CD18. Sequence identity can be determined using a suitable program, such as the Blastx program (Version 1.4), using appropriate parameters, such as default parameters set forth at the NCBI web site ~~(http://www.ncbi.nlm.nih.gov/BLAST/)~~. In one embodiment, parameters for Blastx search are scoring matrix BLOSUM62, W=3. In another embodiment, a functional variant comprises a nucleic acid which has a sequence which differs from the naturally-occurring nucleic acid molecule but which, due to the degeneracy of the genetic code, encodes mammalian CD18 or a portion or functional variant thereof.

Please delete the paragraph at page 33, line 24, to page 34, line 13, and substitute in place thereof the paragraph amended to read as follows.

The anti-CD18 antibody used in the therapeutic and preventive methods described herein can be any of the types of anti-CD18 antibodies that are described in this disclosure. For example, a whole antibody can be used (e.g. an isolated murine antibody which specifically binds with human CD18). Alternatively, the anti-CD18 antibody can

be a fragment of a whole antibody, such as a Fv, Fab, Fab', or ~~F(abN)~~$_2$-F(ab')$_2$ fragment. The anti-CD18 antibody can be an antibody isolated from a human, from a non-human mammal, from a non-human vertebrate, from a library of random or synthetic antibodies. Furthermore, the anti-CD18 antibody can be an antibody which comprises segments obtained from different sources (i.e. a chimeric antibody). By way of example, the antibody can have complementarity-determining regions which have the amino acid sequence of the same regions of a murine antibody which binds specifically with CD18; the same antibody can have non-complementarity-determining regions (also designated structural, framework, or constant regions) which have amino acid sequences which are derived from one or more human antibodies or from consensus human antibody sequences. This antibody is also an example of a type of humanized antibody (i.e. an antibody in which at least a part of the antibody is derived from a non-human source, but which has been modified such that at least one other part of the antibody is more nearly like a human antibody in terms of its amino acid sequence). Anti-CD18 antibodies which are humanized, using any of the methods described herein or any other method known in the art or hereafter developed, can be used in any of the methods described in this disclosure.

Please delete the paragraph at page 41, lines 21-28, and substitute in place thereof the paragraph amended to read as follows.

Efficacy of treatment was evaluated by use of quantitative angiography at the time of stent placement and at the end of the study, and by immunohistologic and morphometric evaluation of iliac artery tissue. Blood samples were collected periodically for assay of serum mAb levels (pharmacokinetics), leukocyte mAb binding (pharmacodynamics), anti-mAb antiglobulin response (immunogenicity), and for hematology and serum chemistry (safety). Safety was further evaluated by recording

vital signs during infusion and body weights, clinical observations and injection site observations during the test period. Other tissue samples were not ~~be~~ evaluated unless warranted (see Table B).

Please delete the paragraph at page 45, lines 21-26, and substitute in place thereof the paragraph amended to read as follows.

1B4 is a murine IgG2a mAb that recognizes CD18 on human, non-human primate and rabbit neutrophils. 1B4 was produced using a commercially available cell line that makes the antibody (ATCC Accession No. ~~TIB10164~~HB-10164). S-S.1 is a murine IgG2a mAb directed against sheep red blood cells. S-S.1 was produced using a commercially available cell line that makes the antibody (ATCC Accession No. TIB-111) and is being used as an irrelevant isotype-matched control antibody.

Marked-Up Copy of Claims Amended in the Amendment Filed in Response to the Office Action Dated 20 February 2002

2. (Amended) The method of claim 1, wherein the anti-CD18 antibody binds specifically with ~~substantially only~~ the CD18 portion of the protein, but does not bind specifically with the non-CD18 portion of the protein.

3. (Amended) The method of claim 1, wherein the anti-CD18 antibody ~~has an epitopic specificity which is the same as or similar to that of monoclonal antibody 1B4~~ is a competitive inhibitor of the binding of monoclonal antibody 1B4 to human CD18.

9. (Amended) The method of claim 6, wherein binding of the anti-CD18 antibody with the antigen inhibits binding of a ~~natural~~ known ligand of the antigen ~~therewith~~ with the CD18 portion of the protein.

12. (Amended) The method of claim 1, wherein binding of the anti-CD18 antibody with the CD18 portion of the protein modulates at least one function normally associated with binding of a natural ligand of the protein therewith.

22. (Amended) The method of claim 21, wherein the antibody fragment is selected from the group consisting of Fv, Fab, Fab', and ~~F(abN)$_2$~~ F(ab')$_2$ fragments.